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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,377	02/26/2002	Catherine Defrenne	BM45379	4141

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EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,377	DEFRENNE ET AL.	
	Examiner	Art Unit	
	Padmavathi v Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,27,29,31,32,35,40,41,43 and 47-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,27,29,31,32,35,40,41,43 and 47-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/15/ 04 has been entered

Amendment

2. Applicant's amendment filed on 12/15/ 04 is acknowledged.

Status of Claims

3. New claims 52-56 have been added.

Claims 25, 27, 29, 31, 32, 35, 40, 41, 43 and 47-56 are pending in the application.

Claim Rejection - 35 U.S. C. 112, first paragraph maintained

4. The rejection of claims 25, 29, 31, 35, 40, 41, 43, 47-51 and newly added claims 52-54 and 56 is maintained as set forth in the previous office action under 35 U.5.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising the amino acid sequence SEQ ID NO: 2, said polypeptide is a recombinant polypeptide, a fusion protein comprising the amino acid sequence SEQ.ID.NO: 2, an immunogenic composition comprising the amino acid sequence SEQ.ID.NO: 2 and a pharmaceutically acceptable carrier, an isolated polypeptide consisting of an immunogenic fragment sequence of 15 or 20 amino acids of SEQ.ID.NO: 2 does not reasonably provide enablement for a polypeptide comprising an immunogenic fragment sequence of at least 15 or 20 amino acids of SEQ.ID.NO: 2, where in the immunogenic fragment , when administered to a subject in a suitable composition which can include an adjuvant, or suitable carrier coupled to

response that recognizes the polypeptide SEQ.ID.NO: 2 is maintained as set forth in the previous office action.

The claims are drawn to an isolated polypeptide and a method for inducing an immune response comprising a member selected from the group consisting of (a) the amino acid sequence SEQ.ID.NO: 2; (b) an immunogenic fragment comprising at least 15 or 20 (the examiner is considering these as fragments) contiguous amino acids of SEQ.ID.NO: 2, where in the isolated polypeptide, when administered to a subject in a suitable composition which can include an adjuvant, or suitable carrier coupled to the polypeptide, induces an antibody or T-cell response that recognizes the polypeptide SEQ.ID.NO: 2. Claims are also drawn to a recombinant polypeptide comprising the amino acid sequence SEQ.ID.NO: 2 and fragments of said polypeptide.

The instant claims are evaluated for scope of enablement based on the Wands analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731,8 USPQ2d 1400 (Fed.Circ.1988) as follows:

(1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The nature of the disclosed invention is an isolated polypeptide of SEQ ID NO: 2 from *Neisseria mengitidis* ATCC 13090 strain which is designated as a " BASB082" polypeptide in examples 1-5. The specification teaches that this polypeptide has been obtained by recombinant cloning and contains 758 amino acids. However, the specification is silent in disclosing whether this polypeptide recognizes antibodies that are obtained from Neisseria infected individuals. Further, the specification fails to indicate or teach any description of fragments of said polypeptide that are able to bind to antisera raised against full-length polypeptide and provides no working examples demonstrating (i.e., guidance) enablement for any *fragments and* uses of the claimed polypeptide.

The state of the prior art indicates that protein chemistry is probably one of the most unpredictable areas of biotechnology and is highly complex. As taught by the prior art (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6), the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis. The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol. 1991, 5(7): 1755-67) teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis

which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition.

In addition to the art-recognized unpredictability, the specification has not provided any guidance as to how an artisan would have fragments that have functional properties in immunological recognition. The specification, however, provides no guidance demonstrating enablement for making and using the claimed fragments. Thus, making and using fragments of a polypeptide must be considered highly unpredictable, requiring a specific demonstration. Absent such demonstration, the skilled artisan would be forced into undue experimentation to make and use the invention commensurate in scope with these claims.

Applicants' arguments filed on 12/15/04 have been fully considered but they are not deemed to be persuasive.

Applicant states that i) the instant application provides full disclosure of the amino acid sequence SEQ.ID.NO: 2 and the nucleotide sequence SEQ.ID.NO: 1, which encodes the polypeptide SEQ.ID.NO: 2 ii) substantial guidance has been provided in specification on pages 45-47 and also one of ordinary skill in the art has ability and skill to produce fragments iii) the examiner's concerns regarding "unlimited and unknown amino acids" of SEQ.ID.NO: 2 are misplaced and the claims do not encompass unlimited and unknown amino acids" because applicant is claiming immunogenic fragments of SEQ.ID.NO:2 and claims are properly enabled.

The examiner understands that the specification discloses the SEQ.ID.NO: 2 and therefore, applicants are enabled for an immunogenic fragment **consisting** of 15 or 20 contiguous amino acids of SEQ.ID.NO: 2, wherein the isolated polypeptide, when administered to a subject in a suitable composition which can include an adjuvant, or suitable carrier coupled to the polypeptide, induces an antibody or T-cell response that recognizes the polypeptide SEQ.ID.NO: 2. However, the specification does not disclose an immunogenic fragment **comprising at least** 15 or 20 contiguous amino acids of SEQ.ID.NO: 2 as claimed and these fragments are broader than SEQ.ID.NO: 2.

With respect to fragments of said polypeptide, the examiner understands that the specification teaches the amino acid sequence SEQ.ID.NO: 2 and therefore enabled for an isolated polypeptide consisting of an immunogenic fragment of 15 or 20 contiguous amino acids of SEQ.ID.NO: 2. However, applicant is claiming an isolated polypeptide comprising of at least 15 or 20 contiguous amino acids of SEQ.ID.NO: 2. Recitation of open language " comprising " in the claims does not limit to the fragments of SEQ.ID.NO: 2 but reads on fragments of SEQ.ID.NO: 2 plus other unknown and unlimited amino acids and are not supported by the present specification, pages 45-47.

With respect to the unpredictability of protein chemistry, applicant noted the art recognized difficulties in processing (via antigen presenting cell) the fragments for inducing a T-cell response. Further applicant states that methods were available to overcome these difficulties at the time of the filing of the instant application for example in Reece et al, Exhibit A the difficulties of protein processing were overcome by synthesizing overlapping dodecapeptides on pins to map T-cell epitopes of tetanus toxin. Pools of 20 peptides were used to simplify the mapping assays. Thus, it was practical to synthesize a large number of peptides, and the initial screen needed only to assay sixty to seventy pools. Pools that generated strong responses were deconvoluted by assaying the members of the pool and such multipin methods were taught in the art such as Current Protocols in Immunology, 1997 (Exhibit B) and Reece et al. 172 J. Immunol. 1994 241 (Exhibit C). Applicant states that the examiner's concerns regarding "unlimited and unknown amino acids" of SEQ.ID.NO: 2 are misplaced.

The examiner has reviewed exhibits A, B and C carefully and understands that epitope mapping using overlapping synthetic peptide pools and assaying such pools using multipin method are known in the art. Here, the issue here is whether immunogenic fragment **comprising** of at least 15 or 20 contiguous amino acids of SEQ.ID.NO: 2 as claimed is enabled

or not. As discussed above, applicant is enabled only for immunogenic fragment consisting of 15 and 20 contiguous amino acids of SEQ.ID.NO: 2. The art submitted by the applicant also clearly indicates that specific small peptides are important in epitope mapping and thus supporting the examiner's position (i.e., **immunogenic fragment consisting of 15 or 20 contiguous amino acid of SEQ.ID.NO: 2**). Further, the art teaches that the longer the peptide, the lower will be the purity of the peptide and synthesis of peptides longer than 20 residues should be avoided (see Exhibit B, unit 9.7.5, third paragraph under assessing peptide sequences). Exhibit C teaches that many epitopes (see abstract) would be missed if the peptides used were long (31mer, Table 2). Thus, the art teaches the specific peptide is critical for identifying successful T-helper epitope and therefore, immunogenic fragment consisting of 1-15 or 1-20 contiguous amino acids of SEQ.ID.NO: 2 are suitable for mapping but not the polypeptide **comprising** an immunogenic fragment of "**at least**" 15 and 20 contiguous amino acids as it reads on unknown fragments that are broader than SEQ.ID.NO: 2.

Applicant is not claiming peptides **consisting of 15 or 20 amino acids of SEQ.ID.NO: 2** but claiming an isolated polypeptide **comprising** an immunogenic fragment of "**at least**" 15 and 20 contiguous amino acids of SEQ.ID.NO: 2. The limitation "at least " in the claims does not limit to 15 and 20 contiguous amino acids but reads on fragments having more than 20 amino acids in length. Similarly the limitation "comprising" leaves " the claim open for the inclusion of unspecified ingredients even in major amounts and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. Therefore, the claimed immunogenic fragment is larger than 20 amino acids (15 or 20 amino acids plus unlimited amino acids) in length. Hence examiner's concern regarding the language used is important in claiming immunogenic fragments.

Evidentiary references as discussed above clearly indicated the use of short 12 –20 mer peptide sequences for mapping and screening epitopes of a larger protein (i.e., fragment **consisting** of 15/20 contiguous amino acid sequence of SEQ.ID.NO: 2) to reveal immunodominant regions of the antigen. In addition, Molloy et al (Molecular Immunol. 35, 1998, pages 73-81) teach, production of TCR (TCR comprising two other immunoglobulin super family member proteins) epitope has remained problematic as the majority of the recombinant proteins remain insoluble and are not processed. Therefore, the claimed isolated recombinant polypeptide comprising an immunogenic fragment of at least 15 or 20 contiguous amino acids of SEQ.ID.NO: 2 (a larger immunogenic fragment) for mapping t-cell epitopes must be considered highly unpredictable requiring a specific demonstration of efficacy of the polypeptide in mapping epitopes. Absent such demonstration, the invention would require undue experimentation to practice as claimed.

New Claim Rejections

Claim Rejections-35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 51, 54 and 40 are rejected as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claims 51 and 54 are drawn to an immunogenic composition comprising the isolated polypeptide of claim 29 and 52 respectively. However, claims 29 and 52 depend on claim 25, drawn to isolated polypeptide. Therefore, there is no difference in the scope of the claimed

polypeptide (claim 25) and immunogenic composition (claims 51 and 54) since both of them comprise the same isolated polypeptide.

Claim 40 is drawn to an immunogenic composition comprising the isolated polypeptide of claim 25 and a pharmaceutically acceptable carrier. However, claim 25 (b) drawn to isolated polypeptide comprising an immunogenic fragment and suitable carrier. Therefore, there is no difference in the scope of the claimed polypeptide 25 (b) and immunogenic composition of claim 40 since both of them comprise the same isolated polypeptide and a carrier.

Claim 40 is unclear because which polypeptide (a) or polypeptide (b) is being claimed is not known.

Claim Rejections - 35 USC 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -- -

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 25, 27, 29, 31, 35, 40, 41, 43 and 47-56 rejected under 35 U.S.C. 102(a) as being anticipated by Wedege et al Infect Immun. 1998 Jul; 66(7): 3223-31.

The claims are drawn to an isolated polypeptide and a method for inducing an immune response comprising a member selected from the group consisting of (a) the amino acid sequence SEQ.ID.NO: 2; (b) an immunogenic fragment comprising at least 15 or 20 (the examiner is considering these as fragments) contiguous amino acids of SEQ.ID.NO: 2, where in the isolated polypeptide, when administered to a subject in a suitable composition which can include an adjuvant, or suitable carrier coupled to the polypeptide, induces an antibody or T-cell response that recognizes the polypeptide SEQ.ID.NO: 2. Claims are also drawn to a recombinant polypeptide comprising the amino acid sequence SEQ.ID.NO: 2.

The transitional limitation "comprises" similar to the limitations, such as, "has", "includes," "contains," or "characterized by," represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Molecular Research Corp. v. CBS, Inc., 793 F2d 1261, 229 USPQ 805 (Fed. Cir. 1986); In re*

Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981); Ex parte Davis, 80 USPQ 448, 450 (Bd. App.1948) ("comprising" leaves "the claim open. for the inclusion of unspecified ingredients even in major amounts". On the other hand, the limitation "consisting of represents closed claim language and excludes any element, step, or ingredient not specified in the claim. In *re Gray, 53 F. 2d 520, Il USPQ 255 (CCPA 1931); Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948).*

Wedege et al disclose a vaccine comprising outermembrane vesicles (OMV) isolated from vaccine strains 44/76 as antigen (see page 3224, left column, second paragraph under Immunoblotting). The prior art also discloses a recombinant Pore OMV vaccine.(see 3226, left column, under 80-70kDantigens). After electro transfer, the OMV proteins from these two vaccine preparations were blotted with serum obtained from vaccinated individuals. Table 2 shows an isolated polypeptide 80kD antigen reacted with IgG antibodies obtained from sera taken from individuals after immunization. The 80kD antigen from OMV vaccine reads on claims 25, 27, 31, and 35 because the art discloses a vaccine OMV comprises 80kD antigen which appears to be similar to the claimed product polypeptide. Therefore, it is inherent that the 80 kD OMV antigen comprises the claimed polypeptide and immunogenic fragments as claimed in 25, 27, 31, 35 because characteristics such as amino acid sequence SEQ.ID.NO: 2 is inherent in the preparation of vaccine comprising isolated polypeptide 80kD OMV vaccine and thus read on the claimed invention including immunogenic composition (claims 40, 41) and a method for inducing an immune response (claim 43) because vaccine is given to human volunteers and the sera obtained after vaccine reacted with 80kD antigen (see Table 2) and thus it elicits the production of antibody IgG etc (see page 3225, right column through page 3226). The isolated antigen 80 kD meet the limitations of the claims 25, 27, 31, 35 because the broadly claimed polypeptide having 758 amino acids is equivalent to 80 kD of the prior art disclosed protein since each amino acid molecular weight is 110 daltons. When producing OMV

vaccine, the composition would inherently contain more than one polypeptide (fusion proteins) and a carrier present, i.e., buffer for pharmaceutical use as required by claims 35 and 40. Therefore, the composition comprising an isolated 80 kD polypeptide in buffer read on immunogenic composition of the claimed invention. Since vaccine comprises more than one antigen it reads on the claim 43.

The prior art also discloses recombinant PorA OMV vaccine (see page 3226, left column under 80-70kD antigen), which contains 80kD antigen (see table 2) and thus reads the recombinant polypeptide, immunogenic composition comprising SEQ.ID.NO: 2 and a fusion protein comprising said polypeptide as claimed in claims 47-56 for the same reasons as discussed above.

In the absence of evidence to the contrary the disclosed prior art OMV vaccine, recombinant PorA vaccine and composition comprising said protein and the claimed polypeptide and immunogenic composition are the same. Since the Office does not have the facilities for examining and comparing applicants' claimed isolated immunogenic polypeptide comprising a polypeptide comprising an amino acid sequence SEQ.ID.NO: 2, composition comprising said polypeptide with the 80kD protein and composition comprising said protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed isolated or recombinant immunogenic polypeptide, vaccine composition comprising said polypeptide and 80kD protein and composition of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Status of Claims

8. No claims are allowed.

Conclusion

9. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives

transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Padma Baskar Ph.D.

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